



Research report

The role of medial prefrontal cortex in theory of mind: A deep rTMS study

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ABSTRACT

Neuroimaging studies suggest that the medial prefrontal cortex (mPFC) plays a central role in cognitive theory of mind (ToM). This can be assessed more definitively, however, using repetitive transcranial magnetic stimulation (rTMS). Sixteen healthy participants (10 females, 6 males) completed tasks assessing cognitive and affective ToM following low-frequency deep rTMS to bilateral mPFC in active-stimulation and placebo-stimulation sessions. There was no effect of deep rTMS on either cognitive or affective ToM performance. When examining self-reported empathy, however, there was evidence for a double dissociation: deep rTMS disrupted affective ToM performance for those with high self-reported empathy, but improved affective ToM performance for those with low self-reported empathy. mPFC appears to play a role in affective ToM processing, but the present study suggest that stimulation outcomes are dependent on baseline empathic abilities.

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1. Introduction

Theory of mind (ToM) refers to the ability to represent and understand another person's psychological perspective by attributing mental states such as beliefs, intentions, emotions, and desires [1]. Considered the foundation of understanding and successfully navigating our social world [2], researchers differentiate between cognitive ToM, which involves understanding others' cognitive mental states such as beliefs and intentions, and affective ToM, which involves comprehending others' emotional states [3]. Impairments in ToM appear to contribute to social and communicative impairments characteristic of individuals with autism spectrum disorders (ASD) [4].

Neuroimaging studies have identified a number of brain regions activated during the performance of ToM tasks (e.g., superior temporal sulcus, temporal poles, temporoparietal junction) [5]. For studies employing cognitive ToM tasks, a dorsal region within the medial prefrontal cortex (mPFC) has been implicated in the vast majority of neuroimaging studies [6]. It is therefore thought to be the crucial region for cognitive ToM, with other activated regions

servicing more general cognitive functions. By contrast, affective ToM tasks appear to activate more ventral regions of the medial prefrontal cortex [7].

Although these findings give a strong indication of the involvement of critical regions, the role of the mPFC in ToM can be more definitively confirmed through the use of repetitive transcranial magnetic stimulation (rTMS). Briefly, when administered at a low-frequency (≤ 1 Hz), rTMS can be used to disrupt cortical activity, and any impact on subsequent task performance gives a reliable indication that the disrupted brain region is crucial for abilities required for task completion [8]. For example, rTMS to right inferior frontal gyrus has been used to demonstrate that region's importance in response inhibition [9].

Although not involving the mPFC, Kalbe et al. [10] administered 1 Hz rTMS to the right dorsolateral prefrontal cortex of healthy males and found decreased response time to cognitive (but not affective) ToM items. The region of the mPFC that has been implicated in cognitive ToM, however, is more difficult to assess using standard rTMS coils, as it is too far below the scalp to allow direct and effective stimulation. The advent of deep TMS techniques, however, in which magnetic stimulation can be delivered to deeper brain structures, means that it is now possible to assess the role of mPFC in ToM via rTMS. Recently, Lev-Ran et al. [11] found that low-frequency deep rTMS to ventral and dorsal regions of the mPFC, using a double cone-coil, impacted upon healthy controls' response time for affective ToM performance, thereby impairing task learning. The current study assessed the acute impact of placebo-controlled low-frequency (1 Hz) deep rTMS to bilateral mPFC on cognitive and affective ToM performance. Based on the

Abbreviations: ToM, theory of mind; ASD, autism spectrum disorders; rTMS, repetitive transcranial magnetic stimulation; mPFC, medial prefrontal cortex; RT, response time; RMET, Reading the Mind in the Eyes Test; EQ, empathy quotient.

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neuroimaging literature, it was hypothesized that active deep rTMS would result in reduced accuracy and increased response time (RT) on a cognitive theory of mind task, but (given primary stimulation of dorsal regions) not affect performance on affective theory of mind tasks. Given the presumed overlap between ToM and general empathic abilities, we also hypothesized that the impact of deep TMS on ToM would be moderated by self-reported empathy.

2. Material and methods

2.1. Participants

Sixteen neurotypical participants, 10 females ($M = 25.67$ years; $SD = 2.34$) and 6 males ($M = 27.67$ years; $SD = 5.23$) aged between 18 and 40, were recruited via advertisements within Monash University and The Alfred Hospital. Participants had no history of neurological or psychiatric disorders (as determined via self-report), and were educated to at least undergraduate level (first-year undergraduate to doctoral level). Mean score on the empathy quotient (EQ; described below) was 48.06 ($SD = 14.96$), which is very similar to that reported in other samples of healthy adults [12,13]. Prior to participation, all participants gave written informed consent and completed an rTMS safety-screening questionnaire. The study was approved by the Human Research Ethics Committees of The Alfred, Monash University, and Southern Health.

2.2. Procedure

Participants completed two sessions at least one week apart. One session involved the administration of active deep rTMS, while the other involved the administration of sham (i.e., placebo) rTMS. Half of the participants received active deep rTMS for their first session. Participants were blind to the stimulation condition.

Deep rTMS was administered via a custom made HAUT-coil (Brainsway Ltd), designed to stimulate bilateral mPFC to a depth of 4–5 cm below the scalp, connected to a Magstim Rapid stimulator (Magstim Co, Wales, UK). This coil was chosen as it is able to provide extensive stimulation of our region of interest (mPFC; see Fig. 1 for field distribution, which indicates the induction of a wide stimulation region primarily affecting dorsal regions of mPFC), but is generally associated with a less substantial scalp muscle contraction and less pain induction relative to the alternative double cone-coil that some of us used in a previous study by Lev-Ran et al. [11]. Resting motor threshold (RMT) was defined as the minimum stimulation intensity of the primary motor cortex (M1) required to produce an observable hand muscle response in 3/5 consecutive trials. For mPFC stimulation, the deep rTMS coil was placed over the site of stimulation, which was defined by the manufacturers as the scalp position 7 cm anterior to M1 along the midline. As noted, field modeling by the manufacturers (Fig. 1) indicates that this position provides relatively wide bilateral stimulation of regions comprising mPFC. Fifteen minutes of either sham or active deep rTMS was then delivered. This involved a single train of 900 pulses at 1 Hz at

100% RMT. The sham condition involved a simulated sound and scalp sensation, but without the delivery of magnetic stimulation into the brain itself.

Immediately following rTMS, participants were administered two computerized ToM tasks (presented via E-prime 2.0).

2.2.1. Affective ToM: Reading the Mind in the Eyes Test (RMET) – Revised: adult version [14]

The RMET is widely considered an affective ToM task. It involves the presentation of 36 photographs of the eye region of male and female actors, flanked by four emotional terms (one correct and three incorrect). In the present study, participants were shown each photograph and asked to choose which word they thought best described what the person in the photograph was thinking or feeling by pressing the keyboard letter (key) corresponding to the location of that word on the screen (top left, top right, bottom left, bottom right). All keys were covered except i, m, r, and c. A key press resulted in the immediate presentation of the next item. Item presentation was randomized. Both RT (ms) and accuracy were recorded. The RMET has been found to successfully discriminate between ASD and neurotypical controls, and has good convergent and discriminant validity [14].

2.2.2. Cognitive and affective ToM: Yoni task [7]

The Yoni task consists of 98 trials designed to separately assess cognitive and affective ToM. In each trial, a cartoon face (Yoni) is presented in the middle of the screen. Four images with a common category (e.g., fruit) surround Yoni, and an incomplete sentence is presented at the top of the screen. Participants are required to read the sentence and click the cursor, using a mouse, on the image that they believe correctly answers the question (based on an analysis of Yoni's non-verbal cues such as eye gaze and facial expression). There are items assessing physical understanding (i.e., as a control condition), cognitive ToM, and affective ToM. Participants' accuracy and RT (ms) were recorded. The Yoni task has been shown to successfully differentiate between cognitive and affective ToM in individuals with lesions affecting circumscribed regions thought to be related to those abilities [7].

These tasks took between 10 and 15 min to complete. The order of the tasks was counter-balanced within and across participants. In order to conduct exploratory analysis on the potential modulating role of empathic ability, all participants completed the self-report EQ [12] at the end of the first session. A higher score on this measure indicates greater empathy.

2.3. Statistical analysis

Data were analyzed using SPSS v18.0, having first been inspected for adherence to assumptions of analysis of variance (ANOVA). Outliers, of which there were a total of eight across all variables, were detected and changed to the one unit above or below the next most extreme (but non-outlying) value. Repeated measures ANOVA was used to compare active and sham conditions for each variable. To determine the influence of self-reported empathy, these analyses were repeated with the addition of self-reported empathy (total score on the EQ) as a covariate (repeated measures analysis of covariance).

3. Results

Summary data are presented in Table 1. There was no difference between active and sham conditions for the Yoni cognitive ToM items for either accuracy $F(1, 15) = 0.31, p = .59$, or RT, $F(1, 15) = 0.25, p = .63$, indicating that deep rTMS did not affect cognitive ToM performance. Similarly, there was no effect of rTMS for the Yoni task affective ToM items for either accuracy $F(1, 15) = 0.59, p = .46$ or RT,

Table 1
Summary data for the Yoni task and RMET (accuracy and response times [RT]).

Task	Condition			
	Sham		Active	
	M	SD	M	SD
Yoni cognitive				
Total correct	32.56	3.67	33.00	3.35
RT (ms)	3717	1789	4089	1911
Yoni affective				
Total correct	36.75	3.87	37.25	3.34
RT (ms)	4741	1328	4352	1166
Yoni physical				
Total correct	18.19	1.97	18.75	1.24
RT (ms)	4316	1632	3692	959
RMET				
Total correct	26.38	3.46	26.38	4.40
RT (ms)	6062	1267	6258	1347

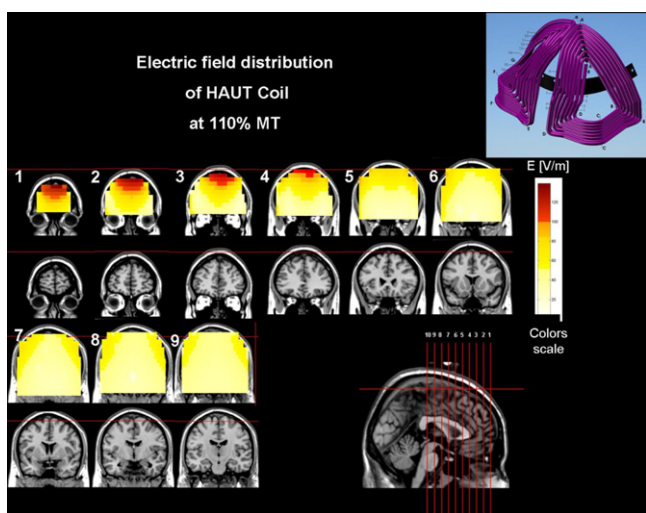


Fig. 1. Colored field maps for the HAUT01-coil indicating the electrical field absolute magnitude in each pixel, for 9 coronal slices 1 cm apart. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m. The field maps are adjusted for stimulator power output of 47%, which was the level required to obtain 110% of the threshold (110 V/m), at a depth of 1.5 cm from coil center. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

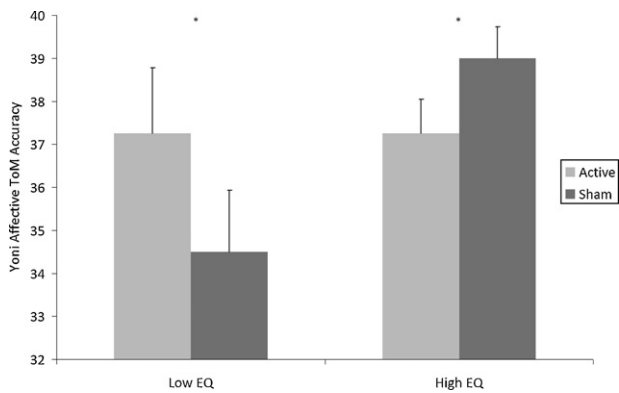


Fig. 2. Self-reported empathy modulates the effect of deep rTMS on affective ToM, having a disruptive influence among those with high EQ but a facilitatory influence among those with low EQ (total correct means + SE) (* $p = .001$).

$F(1, 15) = 2.39, p = .14$, indicating that deep rTMS condition did not impact on Yoni affective task performance. There was no difference between active and sham conditions for the RMET for either accuracy $F(1, 15) = .00, p = 1.00$, or RT, $F(1, 15) = .17, p = .68$.

The inclusion of the EQ total score as a covariate resulted in a significant effect of deep rTMS condition on the Yoni task affective ToM accuracy, $F(1, 14) = 13.37, p = .003$. To further explore this effect, we conducted a median split to derive two groups: high EQ ($M = 59.75, SD = 6.23$) and low EQ ($M = 36.38, SD = 11.34$). There were four females and four males in the low EQ group, and two males and six females in the high EQ group, $\chi^2 = 1.07, p = .302$. A subsequent 2 (rTMS: sham versus active) \times 2 (EQ: high versus low) repeated measures ANOVA revealed a significant interaction effect for the Yoni task affective ToM component, $F(1, 14) = 54.00, p < .001$. Follow-up comparisons revealed that active deep rTMS decreased Yoni task affective ToM among those with high EQ, $F(1, 7) = 31.18, p = .001, d = 0.81$, but increased Yoni task affective ToM among those with low EQ, $F(1, 7) = 27.32, p = .001, d = 0.66$ (see Fig. 2). To illustrate further there was, as expected, an effect for the sham condition for the Yoni task affective ToM component, with high EQ participants revealing greater Yoni task affective ToM accuracy than low EQ participants $F(1, 15) = 7.88, p = .014, d = 1.40$, but following active deep rTMS there was no such difference, $F(1, 15) = 0.00, p = 1.00, d = 0.00$. There was no relationship between EQ group and changes on the other measures of ToM.

4. Discussion

Deep rTMS to the mPFC (as indicated by field maps) did not have an influence on overall task performance for either cognitive or affective ToM. When examining the impact of deep rTMS according to self-reported empathy, however, there was a differential effect on affective ToM. Specifically, deep rTMS reduced affective ToM performance among those with high self-reported empathy, but actually increased affective ToM performance among those with low self-reported empathy.

That there was no overall effect on cognitive ToM was unexpected, and somewhat challenges the central role of the mPFC in cognitive ToM. It is likely that this region acts in concert with other neural regions to facilitate an understanding of others' cognitive mental states, and that reduced excitability in one region by 1 Hz rTMS does not sufficiently disrupt this network. This may be particularly relevant within the present experimental paradigm, as the superior temporal sulcus (STS), for example, has been identified as a key structure for interpreting socially-salient non-verbal and facial cues such as eye gaze direction [15,16], which may be important for success in both the Yoni task and the RMET. It may also highlight the relative importance of functional connectivity

between certain neural structures, rather than the specific sites themselves, in facilitating ToM processing. Indeed, social impairments associated with ToM deficits in ASD have been linked to abnormal neural connectivity (including that involving dorsal and ventral medial prefrontal cortices [17–19]), while there are a number of studies supporting impaired connectivity, particularly across disparate brain regions, among individuals with ASD [20–25]. It is possible that impaired connectivity in ASD creates a cascade effect whereby reduced connectivity between certain key areas essentially creates a bottleneck situation that prevents information from being passed along, resulting in ToM impairments. Interestingly, there is also research among healthy adults linking enhanced connectivity between anterior cingulate cortex and insula with lower observer-rated autism-related social traits [26].

That deep rTMS did not influence overall affective ToM was perhaps less surprising, as neuroimaging studies implicate ventromedial (rather than dorsomedial) prefrontal cortex, and field mapping of our deep rTMS suggest that direct stimulation of ventromedial regions was unlikely (although possible, especially if higher stimulation intensity would have been used). There was, however, a double dissociation when self-reported empathy was taken into account: deep rTMS disrupted affective ToM accuracy among those with higher levels of empathy, but enhanced affective ToM accuracy among those with lower levels of empathy. It is important to note that this was a sample of healthy controls, and the mean EQ score for the low EQ group is still comfortably higher than the clinical cut-off (i.e., autism) score of 30 points.

These results provide further evidence that mPFC plays a role in affective ToM processing. The vmPFC has been consistently implicated in affective ToM [6], with vmPFC damage associated with impaired affective ToM performance as well as reduced empathic abilities and social impairments [27]. Activity in the vmPFC is thought to facilitate automatic aspects of social cognition [28] through the evaluation and regulation of incoming limbic information, which is used to inhibit behavior, regulate emotions, and empathize with others [3]. As there are strong connections between dorsal and ventral regions of the medial prefrontal cortex [29], the present results might indicate that the dorsal regions of mPFC, which were presumably stimulated directly in the current study, is associated with affective ToM performance through its connections with the vmPFC. In this respect, dorsal regions of mPFC may modulate the affective network by managing the flow of information to and from emotion-related areas such as the ventral mPFC. The differential pattern of results as a function of empathy indicates that the dorsal mPFC may play a disparate role in the mediation of affective ToM performance in those with high and low empathy.

There are several possible explanations for this. That reduction in mPFC activity by 1 Hz rTMS actually enhances affective ToM in low EQ individuals might indicate that dorsal regions of mPFC are inhibiting or over-riding ventral regions of mPFC, and disruption of dorsal regions facilitates ToM processing. Similarly, ventral mPFC may ordinarily be underactive among individuals with low empathy, and disruption of dorsal regions of mPFC may allow ventral regions of mPFC to process information to which it would otherwise not have access. Alternatively, individuals with low empathy may have an overactive dorsal mPFC; Lombardo et al. [30] found that being more self-focused, which presumably involves dorsal mPFC [31,32], predicts reduced affective ToM ability among neurotypical adults. Again, reducing this hyperactivity via rTMS may present an opportunity for ventral mPFC regions to operate more effectively. By contrast, functional connectivity between dorsal and ventral regions of the mPFC may play a useful role in affective ToM processing among individuals with higher empathy, and disruption of this network may have produced the decline in performance seen here. Another intriguing possibility is that the effects are specifically related to individual effects of rTMS. For example,

low-frequency rTMS may not reduce activity in all participants; this could be dependent on the basal state of the cortex (which might be reflected in the EQ measure). This basal state may subsequently decide whether rTMS exerts an excitatory or inhibitory influence on cortical activity. Indeed, the effect of stimulation on neurobiological outcomes may depend on spontaneous neural activity and brain states [33]. These explanations, however, are highly speculative, and combined neuroimaging and brain stimulation techniques will be useful for better explaining these findings.

This study is limited by a relatively small sample size, particularly when examining the two empathy subgroups, and should therefore be interpreted with caution. In relation to our null findings, the tasks used may have lacked the necessary sensitivity; for example, effects of reduced mPFC excitability may only be detectable during highly complex cognitive ToM performance, and cognitive ToM ability could be relatively robust to TMS-induced disruption of the mPFC. The use of bilateral stimulation raises additional questions; for instance, there may be laterality effects associated with ToM (e.g., right dlPFC stimulation has been linked to cognitive ToM [10]), and it is possible that bilateral stimulation may have cancelled any such effects. Furthermore, while field maps (Fig. 1) support stimulation of the mPFC in the current study, it is possible that additional brain regions were stimulated, and fMRI-guided neuronavigation to determine site of stimulation may be useful for future studies. Note, however, that anatomical localization was not the purpose of the current study, and that any attempts to localize a brain stimulation technique will be influenced by neural connections of stimulated regions and the indirect spread induced by the stimulation. Nevertheless, functional/structural imaging, including that assessing connectivity, would be a valuable adjunct. It is also possible that the stimulation parameters were too conservative to detect an effect; for example, studies have shown that stimulation above RMT results in more pronounced effects, as does increased duration of stimulation [8]. Related to this, it is possible that any stimulation effects to this region are very short-lived, and although we deliberately chose tasks that could be administered within 10–15 min this may still have been too long. Finally, there may be gender effects associated with the effect of deep rTMS on ToM. Gender was not equally distributed across the two empathy groups; while we lacked the sample size to investigate the effect of gender, it is possible that it has a modulating influence on the reported findings, and is worthy of consideration in future studies.

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